IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

IN RE: CYCLOBENZAPRINE HYDROCHLORIDE EXTENDED-RELEASE CAPSULE PATENT LITIGATION	))))	Civ. No. 09-2118-SLR

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OPINION

Dated: May 12, 2011
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA")[1] by Mylan Pharmaceuticals, Inc. ("Mylan"), Barr Laboratories, Inc. ("Barr"), Impax Laboratories, Inc. ("Impax") and Anchen Pharmaceuticals, Inc. ("Anchen") to market a generic version of the pain drug AMRIX® proprietary to Eurand, Inc ("Eurand") and exclusive licensee Anesta AG ("Anesta") (collectively "plaintiffs"). The active ingredient in AMRIX® is cyclobenzaprine hydrochloride ("cyclobenzaprine") in an extended release formulation, which is protected by, *inter alia*, U.S. Patent Nos. 7,387,793 ("the '793 patent") and 7,544,372 ("the '372 patent"). Upon receiving notification of the filing of Mylan's ANDA, plaintiffs brought this suit for infringement of the '793 and '321 patents pursuant to 35 U.S.C. § 271(e)(2)(A).[2] (D.I. 234 at 3-4) Plaintiffs filed similar suits against Barr, Impax and Anchen. (*Id.*) On December 2, 2009, the cases were consolidated by order of the United States Judicial Panel on Multi-District Litigation. (D.I. 1) Mylan concedes that its generic drug infringes the asserted claims of the patents-in-suit. (D.I. 201) Barr concedes that its generic drug infringes all asserted claims of the patents-in-suit under its claim construction, but not claims 3 and 4 of either patent under plaintiffs' construction. (D.I. 219 at 58:10-13) The parties previously submitted their memoranda on claim construction to the court. From

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[1] Mylan's ANDA application number is 90-738, Barr's is 90-864, Impax's is 90-771, and Anchen's is 91-281.

[2] "(2) It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent[.]"

September 29 to October 7, 2010, a bench trial was held on plaintiffs' claims that defendants infringe the patents-in-suit, and defendants' defenses and counterclaims that the patents-in-suit are invalid and/or unenforceable due to obviousness, indefiniteness, failure to specify the best mode, and/or inequitable conduct.[3] The issues have been fully briefed post-trial. On October 11, 2010, plaintiffs and Impax jointly moved to dismiss Impax, which the court granted on October 13, 2010. (C.A. No. 09-018, D.I. 105) The court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202. Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Parties

1. Eurand is a Nevada corporation with its principal place of business in Vandalia, Ohio. Anesta AG is a Swiss corporation with its principal place of business in Zug, Switzerland. Both companies are involved in research, development and marketing of pharmaceutical drugs.

2. Mylan is a Pennsylvania corporation with its principal place of business in Canonsburg, Pennsylvania. Mylan Pharmaceuticals is a West Virginia corporation with a principal place of business in Morgantown, West Virginia. Mylan Inc. is the parent

[3] During trial, plaintiffs never put on evidence as to Anchen's infringement of the patents-in-suit. In fact, plaintiffs admit that Anchen's current formulation "does not explicitly include one of the plasticizers listed in the claims of the '793 and '372 patents and, thus, does not meet each and every limitation of any of the claims of [the patents]." (D.I. 46 at 3) Therefore, the court grants final judgment in favor of Anchen and against plaintiff.

company of Mylan Pharmaceuticals. Barr Pharmaceuticals is a Delaware corporation with its principal place of business in Pomona, New York. Anchen Pharmaceuticals, Inc. is a California corporation with its principal place of buisness in Irvine, California. Amchen Inc., is a Delaware corporation with its principal place of business in Irvine, California. Mylan, Barr and Amchen are involved in research, development and marketing of pharmaceutical drugs.

B. The Patents and Technology at Issue

3. This case involves an extended release formulation of cyclobenzaprine, a skeletal muscle relaxant which has been available in immediate-release form for over 30 years.

4. Despite existing in immediate release form for over 30 years, plaintiffs were the first to formulate a viable extended relief version of the drug with a pharmacodynamic ("PD") profile that matched its immediate release form.

5. AMRIX® is plaintiff's commercial extended release cyclobenzaprine product.

6. The '793 patent issued June 17, 2008, and is entitled "Modified Release Dosage Forms of Skeletal Muscle Relaxants." The '372 patent issued June 9, 2009 and is also entitled "Modified Release Dosage Forms of Skeletal Muscle Relaxants." The '793 patent discloses an extended release dosage form of cyclopenzaprine, and the '372 patent claims a method for its use. The '372 patent is a divisional patent of the '793 patent, and shares both its specification and much of the structure of its claims.[4] ('372 patent, [52])

[4] Because the patents-in-suit share the same specification, the court will limit its citations to the '793 patent unless noted otherwise.

7. Claim 1 of the '793 patent reads as follows:

1. A multi-particulate pharmaceutical dosage form of a skeletal muscle relaxant providing a modified release profile comprising a population of extended release beads,

wherein said extended release beads comprise

an active-containing core particle comprising a skeletal muscle relaxant selected from the group consisting of cyclobenzaprine, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof; and

an extended release coating comprising a water insoluble polymer membrane surrounding said core,

wherein said dosage form when dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of O.1 N HCl at 37° C exhibits a drug release profile substantially corresponding to the following pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released;

after 8 hours, from about 60-85% of the total active is released;

wherein said dosage form provides therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions when administered to a patient in need thereof; and

wherein said water insoluble polymer membrane comprises a water insoluble polymer selected from the group consisting of ethers of cellulose, esters of cellulose, cellulose acetate, ethyl cellulose, polyvinyl acetate, neutral copolymers based on ethylacrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, pH-insensitive ammonio methacrylic acid copolymers, and mixtures thereof; and a plasticizer selected from the group consisting of triacetin, tributyl citrate, tri-ethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and di -glycerides and mixtures thereof.

('793 patent, col. 10:22-61)

8. Claim 2 depends from claim 1, and reads:

2. The pharmaceutical dosage form of claim 1, wherein said skeletal muscle relaxant comprises cyclobenzaprine hydrochloride.

(*Id.*, col. 10:62-64)

Claim 3 depends from claim 2, and reads:

> 3. The pharmaceutical dosage form of claim 2 wherein said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCL and an AUC_{0-168} within the range of about 80% to 125% of about 740 ng hr/mL and a T_{max} within the range of 80% to 125 % of about 7 hours following oral administration of a single 30 mg cyclobenzaprine HCL MR Capsule.

(*Id.*, col. 10:65-11:5)

9. Claim 4 depends from claim 3, and reads:

> 4. The pharmaceutical dosage form of cliam 3 wherein the adjusted mean ratio of CMR 30 mg/CMR 15 mg is greater than about 2 for each of AUC_{0-168} ($p<0.001$), $AUC_{0-\infty}$ ($p<0.001$), and C_{max} ($p<0.001$).

(*Id.*, col. 11:6-9)

10. Claims 3 and 4 of the '372 patent essentially mirror claims 3 and 4 of the '793 patent. The primary difference between the claims is the substitution of "[t]he pharmaceutical dosage form of claim" for "[t]he method of claim."[5]

11. Barr's proposed generic drug product is a capsule containing multilayer beads. These beads are made of three layers applied atop a sugar core. (PTX-9F BARR_CYC000376-77) Like plaintiffs' product, all beads are manufactured using a fluid bed system with a bottom spray Wurster insert. (JTX-6I, CEPH-AMRIX-00000385)

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[5] For example, claim 3 reads:

> The method of claim 2 wherein said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCl and an AUC_{0-168} within the range of about 80% to 125% of about 740 ng·hr/mL and a T_{max} within the range of 80% to 125% of about 7 hours following a single oral administration a pharmaceutical dosage form comprising 30 mg of cyclobenzaprine HCl.

('372 patent, col. 10:63-11:3)

The first layer contains cyclobenzaprine, dissolved in a mixture of 50/50 acetone and purified water which is then sprayed onto sugar spheres. (*Id.*) The second layer is created by spraying a mixture of Opadry Clear YS-1-7006 and purified water into the drug-layered beads. (*Id.;* PTX-009B at BARR_CYC001822) The beads are then passed through 14-mesh and 24-mesh screens to remove oversized and undersized beads. (*Id.*) This forms an immediate release product. (*Id.*) To form the extended release version, the immediate release beads are further coated with etylcellulose and a plasticizer followed by a heat treatment to dry the beads. (*Id.* at CEPH-AMRIX-00000386) The beads are again passed through 14-mesh and 24-mesh screens to remove oversized and undersized beads. (*Id.*)

C. The Intrinsic Record

12. The patents-in-suit disclose an extended release dosage form of cyclobenzaprine, a method for its manufacturing, and effective dissolution profiles. ('793 patent, col. 5:48-10:20) The patents also include pharmacokenetic ("PK") profiles, identifying dissolution rates and plasma concentrations for both 15 and 30 mg dosage forms. (*Id.*, Figs. 1-7, col. 4:29-43)

13. The specification identifies an *in vitro* dissolution profile, very similar to the profile that appears in claim 1 of the patents-in-suit:

> The dosage form, in accordance with certain embodiments, when disolution tested using United States Pharmacopeia Appratus 2 (paddles @ 50 rpm) in 900 mL of 0.1 N HCL (or a suitable dissolution medium) at 37^{O} C. exhibits a drug relase profile substantially corresponding to the following pattern:
>
> after 2 hours, no more than about 40% of the total active is released;
> after 4 hours, from about 40-65% of the total active is released;
> after 8 hours, from about 60-85% of the total active is released; and
> after 12 hours, from about 75-85% of the total active is released.

(*Id.*, col. 4:36-49)

14. Example 2 discloses a method for making the extended release bead using a fluid bed coater:

> Cyclobenzaprine Hydrochloride (1,200 g) was slowly added to an aqueous solution of polyvinylpyrrolidone such as 25 Povidone USP (K-29/32, 80 g) and mixed well. # 25-30 mesh sugar spheres (2,640 g) were coated with the drug solution in a Glatt fluid bed coater, equipped with a 9" bottom spray Wurster insert to provide IR beads with a coating weight of about 9%. The drug containing particles were dried, and a seal 30 coat of OPADRY® Clear (2% w/w) was first applied and dried in the Glatt fluid bed unit as a precautionary measure to drive off excessive surface moisture. The composition and batch quantities of the IR Beads were given in 5 to 10 kg. Following the second coating process the IR Beads were passed through 14 and 25 mesh screens. Beads remaining on the 14-mesh screen were discarded as oversized beads and beads passing through the 25-mesh screen were discarded as undersized beads.
>
> The next step in the process was to apply an extended release polymer membrane by spraying AQUACOAT® ECD 30, an aqueous dispersion of ethylcellulose with dibutyl sebacate (76:24), onto the IR Beads for a weight gain of approximately 10%. The same fluid bed equipment was used to produce ER (extended release) Beads by further coating the AQUACOAT® coated beads with OPADRY® Clear for a weight gain of 2% w/w prior to curing at 60° C in a conventional oven for a period of 24 hours. The batch size was 5 to 10 kg. The drug release profiles are shown in FIG. 3. The figure also shows the drug release profiles from ER Beads stored in 50 induction sealed HDPE bottles at 25° C/60% RH for 6 months.

(*Id.*, col. 8:23-51)

D. Claim Construction

1. Standards

15. Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence – the claims, specification and prosecution history – because intrinsic evidence is "the most

significant source of the legally operative meaning of disputed claim language." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips,* 415 F.3d at 1313.

16. Claim construction starts with the claims, *id.* at 1312, and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim terms, the terms are presumed to have their ordinary meaning. *Id.* Claims, however, must be read in view of the specification and prosecution history. Indeed, the specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

2. "[A multi-particulate] pharmaceutical dosage form of a skeletal muscle relaxant"

17. Plaintiffs are correct in their assertion that the above phrase from the preamble is limiting. In general, the court will not find a preamble limiting unless there is clear reliance on the preamble in prosecution history, or in situations where it is necessary to provide antecedent basis for the body of the claim. *Symantec Corp. v. Computer Assocs. Int'l*, 522 F.3d 1279, 1288 (Fed. Cir. 2008). Here, the preamble is necessary to provide an antecedent basis for the "said extended release beads" limitation found in the first portion of claim 1. ('793 patent, col. 10:25)

18. Plaintiffs request that the court construe the term "a" as found in the preamble of claim 1 of the patents-in-suit. (D.I. 176 at 7) As demonstrated by plaintiffs,

the Federal Circuit has consistently found "a" to mean "one or more," absent some other form of limiting language. *Silicon Graphics, Inc. v. ATI Techs, Inc.*, 607 F.3d 784, 790-91 (Fed. Cir. 2010); Baldwin *Graphic Sys. Inc. v. Siebert, Inc.* 512 F.3d 1338, 1342-43 (Fed. Cir. 2008); *Free Motion Fitness, Inc. v. Cybex Int'l, Inc.*, 423 F.3d 1343, 1350 (Fed. Cir. 2005). Here, no limiting language exists.

19. Therefore, the court construes this term to mean "a skeletal muscle relaxant drug product with one or more multi-particulate dosage forms."

3. "Cyclobenzaprine, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof"

20. The parties disagree over the scope of the term "derivative." Defendants argue that "derivative" should include "a chemical substance related structurally to another substance and **theoretically** derivable from it." (D.I. 177 at 16) "Claim terms are read [] in the context of the particular claim in which the disputed term appears." *AstraZeneca LP v. Apotex, Inc.*, Civ. No. 2009-1424, - F.3d -, 2010 WL 428624, at *7 (Fed. Cir. Nov. 1, 2010). If the court were to hold that the claim language includes any substance **theoretically** derivable from cyclobenzaprine, it would be ignoring the clear limitation in the claim that the dosage is limited to a "skeletal muscle relaxant." ('793 patent, col. 10:23)[6]

21. Therefore, the court construes this term to mean "cyclobenzaprine base, pharmaceutically acceptable salts thereof such as hydrochloride, muscle relaxant

[6] Under their construction, defendants claim that amitriptyline, an antidepressant, falls within the scope of the claim, as so defined. (D.I. 233 at 22)

derivatives, and mixtures thereof."[7] (*Id.*, col. 6:38-41, 10:23)

4. "Substantially corresponding/corresponds to"

22. The court finds that this term requires no construction. Defendants, in their claim chart, allege that the term is insolubly ambiguous and indefinite, but the court can find no briefing to this effect. (D.I. 163 at 7) Consistent with the Federal Circuit, plaintiffs propose that "substantially corresponding/corresponds to" should have its ordinary meaning as a term of approximation. (D.I. 176) *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002).

5. "About"

23. The term "about" appears in claims 1, 3, and 4 of the patents-in-suit in the context of the concentration of cyclobenzaprine in the bloodstream at a given time, or the percentage of the drug that has been released over a given time. Defendants argue that the term "about" should be construed differently depending on the claim in question. (D.I. 177 at 6-15). With respect to claim 1, defendants contend that the term "about" as it modifies the percentage of the total active ingredient released over time should be limited to plus or minus 5%, because the figures found in the patents "unambiguously illustrate the up-to-5% variance associated with the amount of drug released at the time points in claim 1." (*Id.* at 6-7) With respect to claim 3, defendants argue that the term "about" as it modifies the percentage for various PK parameters should be limited to plus or minus 5% for the same reason as claim 1. (*Id.* at 11) As for

[7] The court's construction of "cyclobenzaprine, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof" is consistent with plaintiffs' proposed construction, except that the court's construction does not include "stereoisomers." As defendants point out, no stereoisomers exist for cyclobenzaprine. (D.I. 277 at 17)

claim 4, defendants argue that the term "about" as it modifies the AUC and C_{max} parameters should be limited to plus or minus the standard deviation found in table 1 of the patents-in-suit. (*Id.* at 14) Defendants further contend that, under plaintiffs' proposed construction, the terms are indefinite. (*Id.* at 8, 12)

24. In contrast, plaintiffs argue that "about" has its ordinary meaning, which is "approximately," and that nothing in the specification is inconsistent with this ordinary meaning. (D.I. 176 at 11-12) Plaintiffs argue that their construction is more consistent as it gives the term "about" the same meaning in every asserted claim. (*Id.* at 13)

25. The court agrees, as defendants' proposed construction improperly imports limitations from the specification into the claims. "The claims, not specification embodiments, define the scope of patent protection. The patentee is entitled to the full scope of his claims, and [the court] will not limit him to his preferred embodiment or import a limitation from the specification into the claims." *Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1348 (Fed. Cir. 2009). Although the term "about," and its ordinary meaning of "approximately," lack the precision found in other terms, such a broad definition has been specifically endorsed by the Federal Circuit. *Merk & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1369 (D. Del. 2005), *see also In Re Brimonide Patent Litigation*, 666 F. Supp. 2d 429, 438 n.7 (D. Del. 2009).

26. Therefore, the court construes this term to have its ordinary meaning of "approximately."

6. "Therapeutically effective plasma concentration"

27. Defendants allege that "therapeutically effective plasma concentration" is

insoluably ambiguous and indefiriite because it is not defined by the patents-in-suit and there is no commonly accepted understanding of the phrase. (D.I. 177 at 18) To the contrary, the Federal Circuit has repeatedly endorsed the use of "therapeutically effective" or "effective amount" as a claim limitation despite its potential for ambiguity. *See, e.g., Geneva Pharm., Inc. v. Glaxosmithkline PLC*, 349 F.3d 1373, 1383-84 (Fed. Cir. 2003) ("Our predecessor court has stated that 'effective amount' is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation.").

28. Therefore, the court construes this term to mean "the amount of a drug required to produce the therapeutic result."[8] *Medicis Pharm. Corp. v. Acella Pharm. Inc.*, Civ. No. 10-1780, 2011 WL 810044, at *5 (D. Ariz. Mar. 2, 2011); *Upjohn Co. v. Riahom Corp.*, 641 F. Supp. 1209, 1219 (D. Del. 1986).

7. The PK limitations of claim 3

29. Plaintiffs ask the court to construe the PK limitations of claim 3 to be arithmetic averages calculated following the oral administration of cyclobenzaprine to subjects in the fasted state, excluding the elderly. (D.I. 176 at 14) Plaintiffs claim that, unless otherwise stated, persons of ordinary skill in the art understand that PK values are reported from clinical studies with subjects in the fasted state when the drug is administered as per FDA guidance. (*Id.;* D.I. 178, ex. 6 at 21; *Id.*, ex. 7 at 70:1-23)

[8] Because the court finds that this term is capable of construction, defendants' indefiriiteness arguments are rendered moot. (D.I. 233 at 47) Similarly, defendants' enablement arguments are rendered moot as the patents need not specifically state what constitutes a therapeutically effective plasma concentration. (*Id.* at 44)

Additionally, persons of ordinary skill in the art would not expect PK values to include elderly subjects when there is a known difference in the PK with respect to the elderly as is the case with cyclobenzaprine. (*Id.*, ex. 7 at 89:16-90:3) Finally, persons of ordinary skill in the art would understand that mean PK values are reported using arithmetic (as opposed to geometric) averages of those values. (*Id.*, at 119:9-25)

30. The court declines to exclude the elderly from the PK values. The specification supports this conclusion, as the specification states that "there is a need for modified release (MR) cyclobenzaprine hydrochloride capsules, 15 and 30 mg, which would substantially minimize intersubject variability and improve quality of life **especially in the elderly population**." ('793 patent, col. 3:43-47) (emphasis added) Further, "[t]he present treatment regimen of 10 mg three times daily is an issue of patient compliance, **especially in the elderly**." (*Id.*, col. 7:59-61) (emphasis added)

31. However, the court does construe the asserted claims to require PK values that are reported using arithmetic averages. While the specification does not describe the values as either arithmetic or geometric, table 1 of the patents-in-suit contains a reference to standard deviation, and there is no dispute that persons of skill in the art do not calculate standard deviations of geometric means. (*Id.*, at 123:16-125:3) The knowledge of one of ordinary skill in the art can provide context to the claims, and can aid the court in resolving ambiguity. *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1332-33 (Fed. Cir. 2010). Here, applying knowledge of one of ordinary skill in the art to give the claims context does not limit the claims, it merely clarifies them.

32. Similarly, the court construes the claims to require PK values that are calculated after oral administration to subjects in a fasted state. Nothing in the

specification implies that the values were calculated in any other way, nor is there any evidence that a person of ordinary skill in the art would understand the calculation to be different absent a clear disclaimer in the patent.

33. Therefore, the court construes this term to require arithmetic averages calculated after the oral administration of cyclobenzaprine to subjects in a fasted state in a population that may include the elderly.

8. "Said active containing core particles comprise from about 7% to about 12% by weight of the water insoluble polymer membrane"

34. The parties agree that claim 6 of the '321 patent contains typographical errors. (D.I. 176 at 19; D.I. 177 at 20) Where no certificate of correction has been issued for a patent, as is the case here, a district court can correct an error through claim construction "only if (1) the correction is not subject to reasonable debate based on consideration of the claim language and the specification; and (2) the prosecution history does not suggest a different interpretation of the claims." *Novo Industries, L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1354 (Fed. Cir. 2003); *accord Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1216 n.8 (Fed. Cir. 2008) (the exception to the rule against redrafting claims is "when there is an obvious administrative or typographical error that is not subject to reasonable debate"). Here there is agreement by the parties as to the nature of the mistake, and defendants do not dispute plaintiffs' representation that the prosecution history does not suggest a different interpretation of the claim. (D.I. 118 at 31; D.I. 128 at 16, n.4)

35. The court construes the claim accordingly, and finds that the typographical errors should be corrected as follows: "said water insoluble polymer membrane on said

active-containing core particles comprises from about 7% to about 12% by weight of said extended release beads."

E. Infringement

1. Standard

36. A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

37. "Direct infringement requires a party to perform each and every step or element of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir.

2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

2. Discussion

38. The court notes that in the present litigation, the active ingredient in both Barr's and plaintiffs' drugs is cyclobenzaprine HCL. (PTX-009E at BARR_CYC000111) In addition, both drugs contain many of the same inactive ingredients including diethyl phtalate, ethylcellulose, and gelatin. (*Id.*)

a. Claim 3

(1) Barr's 30 mg product

39. Barr makes the unusual argument that it does not infringe claims 3 and 4 of the patents-in-suit under plaintiffs' construction, but that it does under its own. (D.I. 219 at 58:8-13) Because the court has construed the disputed terms in claim 3 in a way that is substantially similar to plaintiffs' proposed constructions, it will address infringement.

40. Claim 3 depends from claim 2, and reads:

> 3. The pharmaceutical dosage form of claim 2 wherein said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCL

> and an AUC_{0-168} within the range of **about 80%** to 125% **of about 740 ng hr/mL** and a T_{max} within the range of 80% to 125 % of about 7 hours following oral administration of a single 30 mg cyclobenzaprine HCL MR Capsule.

(*Id.* 10:65-11:5) (emphasis added)

41. Barr contends that, when a single dose of its 30 mg ANDA product is administered to subjects in a fasted state and the PK results are calculated as arithmetic means (consistent with plaintiffs' construction), the AUC_{0-168} of Barr's product is 586.74 ng hr/mL, which is less than 80% of 740 ng hr/mL.[9] (D.I. 237 at 26-27; D.I. 223 at 996:4-998:18) Barr's expert, Dr. Courtney Fletcher ("Fletcher"), opined that, because the ranges in claim 3 relate to a bioequivalence assessment, the FDA guidance on bioequivalence provides the metes and bounds of the claimed ranges; the FDA is clear that 80% means 80% with a two decimal point precision or, in this case, 592.00. (D.I. 223 at 998:19-999:3) Barr argues that neither plaintiffs nor their expert, Dr. Daniel Weiner ("Weiner"), provided any basis for why 586.74 is "about" 592. (D.I. 237 at 26)

42. The court declines to embrace Barr's reasoning. As noted, 80% of 740 ng hr/mL is 592. Barr's proposed construction of "about" 80% was plus or minus 5% of 592 or 562.4. Barr's product has an AUC_{0-168} value of 586.74 ng hr/mL, which is less than 1% less than 592. The court finds that 586.74 is about 80% of 740. Moreover, even constructions of "about" that the Federal Circuit has described as "narrow" are broader than Barr suggests. *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1328 (Fed. Cir. 2007) (affirming a district court's "narrow" construction

[9] Eighty percent (80%) of 740 ng hr/mL is 592.

of the term "about 1:5" as encompassing a range of ratios "no greater than 1:3.6 to 1:7.1"); *UCB, Inc. v. KV Pharm. Co.*, Civ. No. 08-223, 2009 WL 2524519, at *4 (D. Del. Aug. 18, 2009). Finally, bioequivalence is not necessary for patent infringement, and the Federal Circuit has refused to import limitations arising from FDA bioequivalence regulations into a claim, even when an inventor refers to the FDA guidelines in the context of defining the term "equivalent." *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1686-87 (Fed. Cir. 2010)

43. The court finds literal infringement of the patents-in-suit by Barr's 30 mg product.

(2) Barr's 15 mg product

(a) The '793 patent

44. Claim 3 of the '793 patent requires an AUC_{0-168} of about 80% to about 125% of 740 ng hr/mL "following oral administration of a **single 30 mg cyclobenzaprine HCL MR Capsule**." ('793 patent, col. 11:2-5) (emphasis added) Barr's 15 mg product is not a single 30 mg capsule and, therefore, cannot literally infringe claim 3.

45. Likewise, Barr's 15 mg product does not infringe claim 3 under the doctrine of equivalents. Although there is no functional difference between Barr's 15 mg and 30 mg products aside from the number of beads contained within each capsule (D.I. 220 at 396:17-397:2), to find that multiple capsules infringe a claim requiring the administration of a single capsule would vitiate the single capsule limitation, thus violating the all-elements rule. *Amazin' Raisins Int'l, inc. v Ocean Spray Cranberries, Inc.*, 306 Fed. Appx. 553, 558 (Fed. Cir. 2008).

(b) The '372 patent

46. Unlike claim 3 of the '793 patent, claim 3 of the '372 patent requires an AUC_{0-168} of about 80% to about 125% of 740 ng hr/mL "**following a single oral administration [of] a pharmaceutical dosage form** comprising 30 mg of cyclobenzaprine HCL." ('372 patent, col. 11:2-3) (emphasis added) This limitation is markedly different from the limitation in claim 3 of the '793 patent that requires a single "capsule."

47. As shown in Barr's ANDA application and explained by Weiner, there is no functional difference between Barr's 15 mg and 30 mg products aside from the number of beads contained within each capsule. (PTX-9F at BARR_CYC000377; D.I. 220 at 396:17-397:2) The beads in the 15 mg capsule have the same composition by weight as the beads in the 30 mg capsule. (PTX-9F at BARR_CYC000377) The fill weight of a single 15 mg capsule, including drugs, fillers and coatings, is 78.6 mg, exactly half of the 30 mg capsule's 157.2 mg fill weight. (*Id.*) In support of using two 15 mg capsules as a single 30 mg dose, Barr's ANDA application has the following proposed labeling: "[s]ome patients may require up to 30 mg/day given as (1) [] Cyclobenzaprine Hydrochloride Extended-Release 30 mg capsule taken once daily or as (2) Cyclobenzaprine [] Hydrochloride Extended Release 15 mg capsules taken once daily." (PTX-9E at BARR_CYC000121) Thus, Barr contemplates two 15 mg capsules comprising a single 30 mg pharmaceutical dosage form. Given that the contents of the 15 mg capsules are the same as the 30 mg capsules, and the broader "single pharmaceutical dosage form" language of the '372 patent, Barr's 15 mg dosage form literally infringes claim 3 of the '372 patent.

b. Claim 4 of the patents-in-suit

48. As discussed *supra* (¶ 39), Barr only contests infringement of claim 4 of the patents-in-suit under plaintiffs' construction. (D.I. 219 at 58:8-13) Because the court has construed the disputed terms in claim 4 in a way that is substantially similar to plaintiffs' proposed construction, it will address infringement.

49. Barr argues that its products do not infringe claim 4 because claim 4 depends on claim 3, and its products do not infringe claim 3 of either patent. (D.I. 237 at 32) As explained supra (¶¶ 43, 47), Barr's 30 mg product infringes claim 3 of the patents-in-suit, and Barr's 15 mg product infringes claim 3 of the '372 patent. Therefore, the court finds that Barr's 30 mg product literally infringes claim 4 of the patents-in-suit, and Barr's 15 mg product infringes claim 4 of the '372 patent.

F. Validity

1. Obviousness

50. Defendants argue that the asserted claims of the patents-in-suit are obvious in view of other extended release drug formulations like the ones discussed in European Patent Application No. 92109699.6 to Urban ("Urban"), and US Patent No. 6,344,215 ("the '215 patent"), when combined with the known PK parameters of immediate release cyclobenzaprine as disclosed in the prior art, discussed *infra*.

a. Standard

51. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on several underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

52. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In addition to showing that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

53. "Because patents are presumed to be valid, *see* 35 U.S.C. § 282, an alleged infringer seeking to invalidate a patent on obviousness grounds must establish its

obviousness by facts supported by clear and convincing evidence." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) (citation omitted). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)).

b. Prior art

54. **Urban** is a European patent application that discloses a multi-particulate controlled release dosage micropellet with a core containing an active ingredient, a water insoluble polymer and a plasticiser. (DTX-289 at MYLAN_CYCL00000495-96; D.I. 222 751:9-754:5) It published December 16, 1992 and, therefore, is statutory prior art to the patents-in-suit. 35 U.S.C. § 102(b). One application of these micropellets is as "sprinkles" over a food substance. (DTX-289 at MYLAN_CYCL00000496) The micropellets range in size from about 0.42 to about 3.36 mm in diameter, with an optimal size of 0.42-1.19 mm. (*Id.*) Urban discloses several techniques for manufacturing the micropellets in a fluid bed granulator, including: (1) granulating a mixture of a medicament and polymer; (2) drying said granulation; (3) screening the granulation; (4) collecting the screened granulation; (5) coating the collected granulation; (6) drying the coated granulation; (7) coating the coated granulation; and (8) optionally repeating steps (6) and (7). (*Id.*) Urban discloses a dissolution profile for

the produced micropellets when tested in a USP 2 paddle apparatus in a dissolution medium of 900 mL distilled water at 37 degrees Celsius, said water having been dearated with helium, and said apparatus operating with a paddle speed of 100 rpm. (*Id.* at MYLAN_CYCL00000499) After 2 hours, micropellets with two coatings have a 42.8% dissolution rate. (*Id.* at MYLAN_CYCL00000501) After 4 hours, said micropellets have a 64.6% dissolution rate. (*Id.*) After 8 hours, said micropellets have 86% dissolution rate. (*Id.*) Finally, and most important in the context of obviousness, Urban discloses a list of suitable medicaments for use in this extended release formulation, including cyclobenzaprine. (*Id.* at MYLAN_CYCL00000494; D.I. 222 at 723:24-724:22)

55. The **'215 patent**[10] is entitled "Methylphendiate Modified Release Formulations," and it discloses a multi-particulate dosage form of methylphenidate, a drug that shares key properties with cyclobenzaprine, including its dosage amount, ionization, hydrochloride salt structure, and solubility. (D.I. 222 at 764:3-766:6) The '215 patent issued February 5, 2002 from an application filed October 27, 2000 and, therefore, is statutory prior art to the patents-in-suit. 35 U.S.C. § 102(b). The dosage form claimed in the '215 patent contains two populations of beads, one immediate release and one extended release. ('215 patent, col. 1:63-65) The immediate release beads are prepared by adding methylphenidate HCL to an aqueous binder solution such as PVP and applying this formulation to sugar spheres. (*Id.*, col. 4:34-36) The

[10] Dr. Gopi Venkatesh ("Venkatesh"), the inventor of the patents-in-suit, is also a named inventor on the '215 patent and the '215 patent forms the basis for defendants' claim of inequitable conduct, as discussed *infra*.

spheres are then dried and coated with a seal coat of Opadry clear. (*Id.*, col. 4:36-39) The extended release beads are made by applying a layer of extended release membrane coating such as ethylcellulose and a seal coat on the IR beads. (*Id.*, col. 4:44-47) The '215 patent also discloses multiple dissolution profiles, varying by manufacturing technique and percentage of extended release beads to immediate release beads. (*Id.*, claims 1, 4) These dissolution rates are calculated using the same USP apparatus 2 at 50 rpm in 500 mL of water as found in the patents-in-suit. (*Id.*, col. 7:50-51). At 2 hours, a ratio of 20% immediate release and 80% extended release beads has a 29.8% dissolution rate. (*Id.*, claim 1) At 4 hours, this same mixture has a 57.8% dissolution rate. (*Id.*) At 8 hours, the mixture has a 79.2% dissolution rate. (*Id.*) Venkatesh admits that this is the same dissolution profile as claimed in the patents-in-suit. (D.I. 219 at 243:23-244:5)

56. **Hucker** is an article entitled "Plasma levels and bioavialbility of cyclobenzaprine in human subjects," published in The Journal of Clinical Pharmacology in 1977. (DTX269 at FLETCHER-00351) It is statutory prior art to the patents-in-suit. 35 U.S.C. § 102(b). It discusses the results of various dosages of cyclobenzaprine administered both orally and intravenously. (*Id.* at FLETCHER-000353) Importantly, Hucker reveals that the PK profile for cyclobenzaprine is linear. (*Id.* at FLETCHER-000353)

57. **Winchell** is an article entitled "Cyclobenzaprine pharmacokinetics, including the effects of age, gender, and hepatic insufficiency," published in The Journal of Clinical Pharmacology in 2002. It is statutory prior art to the patents-in-suit. 35 U.S.C. § 102(b). Winchell discloses that cyclobenzaprine plasma concentrations increase in

proportion to dose after single and multiple doses of 2.5, 5 and 10 mg. (D.I. 673 at 64) Winchell also discloses that, after dosing patients every 8 hours for 7 days at 10 mg/dose, subjects had a C_{max} of 25.9 ng/mL with a standard deviation of 11.2. (*Id.* at 65) Its AUC_{0-8} ng h/mL is 176.5. (*Id.*)

c. Prima facie case

58. Plaintiffs argue that the invention was not obvious because, before the patents-in-suit, no dosage form of cyclobenzaprine existed that provided a therapeutically effective plasma concentration over a period of 24 hours, nor did PK values for said formulation exist. (D.I. 238 at 10-12) Plaintiffs contend that not every element of every asserted claim of the patents-in-suit was described in the prior art and, thus, the patents could not be obvious. (*Id.*)

59. The court disagrees for several reasons. First, not every limitation of a claimed invention need be found in the prior art in order for said invention to be obvious. The *Graham* factors direct the court to look to the scope and content of the prior art, the differences between the invention and the prior art, and the level of skill of one of skill in the art. *KSR*, 550 U.S. at 406. While it may be easier to prove obviousness if each limitation of the claimed invention is found in the prior art, the level of skill of one of ordinary skill in the art can, at times, fill in the gap when limitations of the claimed invention are not specifically found in the prior art. *Purdue Pharma Products L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 373 (Fed. Cir. 2009).

60. In this regard, cyclobenzaprine existed in immediate release form well before the issuance of the patents-in-suit. (DTX-269) Both the multilayered, extended release delivery system and the claimed dissolution profile were disclosed in the '215

patent.[11] (D.I. 222 751:9-754:5; '215 patent, claim 1; col. 4:34-36) The claimed PK profile was disclosed in the Winchell reference,[12] and optimization of this immediate release profile into an extended release form was routine for one of ordinary skill in the art. (D.I. 673 at 64; D.I. 224 at 1443:4-11; D.I. 219 241:6-246:2) *Purdue Pharma Prods. v. Phar Pharm., Inc.*, 642 F. Supp. 2d, 329, 373 (D. Del. 2009), *aff'd*, 377 Fed. Appx. 978 (Fed. Cir. 2010) (information regarding PK data and target blood plasma profiles for the extended release version of a drug was obvious based on a cited reference in combination with what was generally known about the immediate release version of the drug and controlled release formulations).

61. Plaintiffs argue that cyclobenzaprine has no known PK/PD correlation, thus, converting the PK profile of the immediate release version into an extended release version was not obvious. (D.I. 238 at 26) However, this is contradicted by the testimony of Dr. James Clevenger ("Clevenger"), one of the inventors of the patents-in-suit, who testified that he used the data from the instant release profile of Flexeril® to create the extended release profile found in the patents-in-suit. (D.I. 222 at 946:5-11) "It can be assumed that [the immediate release product] produced a therapeutic effect. So these blood levels if they produce the therapeutic effect, if we get something similar to those blood levels with the [extended release] capsule, then we, too, will have a product that will produce a therapeutic effect." (*Id.* at 6-10) The process was so

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[11] Notably, even FEXERIL®, plaintiffs' immediate release cyclobenzaprine product, produces AUC and C_{max} within the limitations of claims 3 and 4 of the patents-in-suit. (D.I. 224 at 1263:5-1264:15)

[12] Similarly, the linear, dose proportional characteristics of cyclobenzaprine as reflected in claim 4 of the patents-in-suit are disclosed in the Winchell reference.

straightforward that plaintiffs were able to meet their target profiles on the first or second try. (D.I. 219 at 252:8-9)[13]

62. With respect to the claimed T_{max}, Weiner conceded at trial that T_{max} can be calculated by a computer program where, like here, AUC and C_{max} are known. (D.I. 224 981:21-982:2; 991:18-992:7) As the Federal Circuit has said, "the discovery of an optimum value of a variable in a known process is usually obvious." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007). Therefore, the fact that the claimed T_{max} is missing from the prior art does not prevent the court from finding the patents-in-suit to be obvious. The question before the court, then, is whether it would have been obvious for one of skill in the art to combine these known elements, and whether any secondary indicia of nonobviousness exist to overcome the prima facie case of obviousness. *KSR*, 550 U.S. at 406.

63. It would have been obvious to one of skill in the art at the time of the invention to try and create an extended release formulation of cyclobenzaprine mirroring the PK properties of the immediate release formulation. (D.I. 222 at 717:13-718:11) If an extended release formulation matches the AUC and C_{max} of the already approved immediate release formulation, a person of ordinary skill in the art can generally expect that the extended released formulation will have approximately the same effect in the body as the immediate release formulation. (D.I. 222 at 749:5-13; D.I. 223 at 970:20-971:8) Such a motivation is taught by the FDA, in its direction that

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[13] The fact that a claimed value was not disclosed in the prior art is inconsequential to an obviousness analysis where said value would be uncovered via routine experimentation. *Purdue Pharma Products L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 373 (Fed. Cir. 2009).

an extended release dosage form should have the same AUC and C_{max} of an already approved immediate release formulation. (DTX-674 at 15; D.I. 223 at 970:20-971:8) Additionally, it would have been obvious to one of skill in the art to use the invention's claimed drug delivery system, as it had already proven effective with a drug that was related to cyclobenzaprine and shared many of its properties.[14] (D.I. 222 at 764:3-766:6)

64. Therefore, a person of ordinary skill in the art would have been motivated to take a group of known elements to create an extended release version of cyclobenzaprine, and to have a reasonable expectation of success in doing so.[15] The patents-in-suit "claim[] a structure already known in the art that is altered by the mere substitution of one element for another known in the field, [and] the combination [did no] more than yield a predictable result." *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). Therefore, the invention was obvious. *Pfizer, Inc. v. Apotex*, 480 F.3d

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[14] The court notes in this regard that the '215 patent, which claims the extended release delivery system used in the patents-in-suit, was not before the PTO during examination of the '793 patent. Therefore, while defendants must still prove that the patent is obvious by clear and convincing evidence, they do not have the additional burden of overcoming the presumption that is due a qualified government agency presumed to have properly done its job. *Tokai Corp. v. Easton Enters., Inc.*, Civ. No. 2010-1057, - F.3d -, 2011 WL 308370, at *6 (Fed. Cir. Jan. 31, 2011) (citations omitted).

[15] Plaintiffs argue that one of ordinary skill in the art would not have a reasonable expectation of success in making the claimed invention, because no known PK/PD relationship exists for cyclobenzaprine. (D.I. 238 at 23) The lack of a PK/PD relationship is of no moment, however, given that one of ordinary skill in the art would expect the extended release formulation to have the same PD effect on the body if it has the immediate release formulation's PK profile. (D.I. 222 at 749:5-13; D.I. 223 at 970:20-971:8) Because the court does not require a known PK/PD relationship for a finding of obviousness, defendants' written description argument is rendered moot. (D.I. 233 at 46)

1348, 1367 (Fed. Cir. 2007).

d. Secondary considerations

65. Plaintiffs argue that, even if defendants meet their prima facie case of obviousness (which they have), the patents-in-suit are not obvious because of such secondary considerations as failure of others, unexpected results, long-felt need, and commercial success.

(1) Failure of others

66. Plaintiffs contend that ALIZA, one of the leaders in the field of extended release drug delivery systems, failed to make an extended release version of cyclobenzaprine, and that this failure shows that plaintiffs' formulation is non-obvious. (D.I. 238 at 34) However, ALIZA's goals were different than those of plaintiffs. ALIZA's "idea was to not only make [cyclobenzaprine] once a day, but impact the sedation and side effects." (D.I. 219 at 118:11-12) It turned out that there was "a correlation between people who said that the product was efficacious and the people [who] had sedation." (*Id.* at 22-24) In contrast, plaintiffs' goal was to improve compliance through reduced dosing frequency (*Id.* at 186:8-20), not to reduce side effects. (*Id.* at 186:21-23) Therefore, ALIZA's failure is not relevant to an obviousness analysis. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991) (internal citations and quotations omitted); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 494 (D. Del. 2006).

(2) Commercial success

67. In general, commercial success "is only significant if there is a nexus between the claimed invention and the commercial success." *Tokai Corp. v. Easton*

Enters., Inc., 632 F.3d 1358 (Fed. Cir. 2011). Plaintiffs argue that they need not prove a link between the commercial success and the patented invention because there is no dispute that the patent discloses the product. (D.I. 238 at 40); *Ormco Corp. v. Align Tech. Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

68. Plaintiffs have not proven that their product was commercially successful. It is uncontested that, despite spending about $100 million to promote AMRIX® in 2009, its costs exceeded sales by more than $55 million. (D.I. 233 at 450) In addition, defendants have rebutted the presumption of a link between the commercial success of the patented invention because of the fact that plaintiffs' marketing director, Matthew Napoletano, admitted that plaintiffs had a legion of 800 representatives promoting AMRIX® in a "promotionally sensitive market." (D.I. 223 at 1152:14-1153:4) This fact leads the court to find that any commercial success of AMRIX® was linked to a powerful and expansive marketing campaign, rather than its patented features.

(3) Long felt need

69. Plaintiffs have failed to show that AMRIX® represented the fulfillment of a long felt need. Plaintiffs did not present expert testimony on the topic, instead relying on the commercial success of immediate release cyclobenzaprine to show that an ER version was needed. (D.I. 238 at 32) This alone is insufficient to show long felt need and, as in *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 455 (D. Del. 2010), there were other drugs on the market that filled the niche left vacant by the absence of an ER cyclobenzaprine product, thus mitigating the need for one. (D.I. 222 at 664:17-665:20) Moreover, the commercial success of AMRIX® does not support the claimed long felt need, as it has only captured a small percentage of the market despite a

massive marketing campaign. (D.I. 233 at 41)

(4) Unexpected results

70. Plaintiffs argue that AMRIX® produced unexpected results because it has less side effects than the immediate release formulation despite a higher C_{max}. (D.I. 238 at 37) Plaintiffs have no basis for this claim, as their own statisticians have opined that "it is [not] statistically appropriate to claim any significance between [AMRIX®] versus [cyclobenzaprine immediate release]," in the context of lowered side effects. (DTX-486 at 1)

4. Best Mode

71. Defendants argue that the asserted claims are invalid for failure of the inventors to disclose the best mode for making the invention. (D.I. 233 at 48) Specifically, defendants allege that Venkatesh preferred dew points for both coating steps used to make the claimed product, yet the specification makes no mention of the dew point or its importance.

a. Standard

72. The statutory basis for the best mode requirement is found in 35 U.S.C. § 112 ¶ 1, which reads in pertinent part: "The specification . . . shall set forth the best mode contemplated by the inventor for carrying out his invention." "The purpose of the best mode requirement is to ensure that the public, in exchange for the rights given the inventor under the patent laws, obtains from the inventor a full disclosure of the preferred embodiment of the invention." *Dana Corp. v. IPC Ltd. P'ship*, 860 F.2d 415, 418 (Fed. Cir. 1988). Whether a patent meets the best mode requirement is a question of fact. *Zygo Corp. v. Wyko Corp.*, 79 F.3d 1563, 1566-67 (Fed. Cir. 1996) (*citing*

Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1578 (Fed. Cir. 1991)). "Invalidation for failure to set forth the best mode requires (1) the inventor knew of a better mode than was disclosed and (2) the inventor concealed that better mode. Both parts of the best mode test must be met in order to invalidate the patent." *High Concrete Structures, Inc. v. New Enterprise Stone and Lime Co.*, 377 F.3d 1379, 1382 (Fed. Cir. 2004) (citations omitted). "[T]he date for evaluating a best mode disclosure in a continuing application is the date of the earlier application with respect to common subject matter." *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 557 (Fed. Cir. 1994).

b. Discussion

73. In March 2003, prior to the filing of the application for the '793 patent, Venkatesh told the FDA that, during manufacturing, "the dew point of the incoming air was monitored by setting the control at a very low target of 8^{O} C $(6\text{-}12)^{O}$ C," and that "decreasing the dew point of the incoming process air reduced the tackiness of the beads and reduced the tendency of the coated beads from clumping together." (DTX-192 at CEPH0-AMRIX-54557) As described *supra* (¶ 11), if the beads clump together, they are removed as oversized during the screening process that occurs after every coating step. Therefore, as more beads clump together, yield rates decrease.

74. In addition to affecting the yield of the beads, the dew point also adversely affects dissolution. As Venkatesh admitted, "[i]f you don't use the proper optimization, then you may not get good yield or you may not get the proper coating . . . [t]hen the product will not be good." (D.I. 220 at 290:16-23) Years after the filing of the '793 patent, Venkatesh filed a US Patent Application No. 12/314,290, claiming a method of

making the '793 patent's formulation wherein Venkatesh claimed the critical dew point range of about 5-20° C. (PTX 057 at [101]) This application also confirms that a controlled dew point causes the resulting beads to show an improved and uniform dissolution profile. (*Id.* at [55]) ("When IR beads are coated with the ER coating composition under coating conditions . . . in which the temperature and humidity are maintained to provide a dew point of about 5-20° C, . . . the resulting ER beads show improved stability properties. For example, ER beads from commercial capsules, prepared in this manner . . . consistently provide substantially uniform dissolution profiles when tested under *in vitro* conditions.").

75. Plaintiffs make numerous arguments in response to defendants' allegations that Venkatesh concealed his best mode. First, plaintiffs argue that Venkatesh's trial testimony shows that he did not have a subjective belief in a best mode. This testimony, however, is directly contrary to statements made by Venkatesh to the FDA, as well as internal Eurand memoranda illustrating plaintiffs' use of the best mode in 2002-03, well before the '793 patent was filed. (D.I. 240 at 23-24; DTX-192 at CEPH0-AMRIX-54557; DTX-196 at EI58803)

76. Next, plaintiffs argue that the specification of the patents-in-suit enables the allegedly optimal dew point ranges because optimizing dew point ranges is a routine detail of manufacturing. (D.I. 238 at 53; D.I. 222 at 902:3-903:23) In further support of this argument, plaintiffs point out that defendants' own technicians were able to optimize the dew point in just a few days. (D.I. 225 at 1559:25-1570:14)

77. Plaintiffs are correct that "the best mode requirement does not require the disclosure of 'routine details' that would be apparent to one of ordinary skill in the art

practicing the invention." *Liquid Dynamics, Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1223 (Fed. Cir. 2006). In response, defendants' expert, Dr. Paul Jarosz ("Jarosz"), testified that Venkatesh's preferred dew point range is at the extreme low end of the possible spectrum, an unusual practice. (D.I. 221 at 527:17-529:3)

78. Even, assuming, *aguendo*, that Venkatesh's preferred dew point range is at the low end of the possible spectrum, this evidence fails to rise to the clear and convincing standard necessary to invalidate a patent. Illustrative of this failure is Jarosz's concession that: (1) it would be routine to control humidity during product fabrication; (2) the allegedly concealed dew points were within the normal operating range of a commonly used fluid-bed coating device; and (3) Venkatesh's optimal dewpoint was within this normal operating range. (D.I. 221 at 578:8-580:3)

G. Inequitable Conduct

79. Defendants argue that the patents-in-suit are unenforceable due to inequitable conduct for the failure of plaintiffs to disclose the '215 patent to the PTO during the prosecution of the '793 patent. (D.I. 233 at 52) Furthermore, the '372 patent is unenforceable as a result of prosecution counsel's material misrepresentations to the PTO in the form of a false certification made in an information disclosure statement. (*Id.* at 56)

1. Standard

80. Applicants for patents and their legal representatives have a duty of candor, good faith, and honesty in their dealings with the United State Patent and Trademark Office ("PTO"). *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995); 37 C.F.R. § 1.56(a) (2003). The duty of candor, good faith and honesty includes the duty

to submit truthful information and the duty to disclose to the PTO information known to the patent applicants or their attorneys which is material to the examination of the patent application. *Elk Corp. of Dallas v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed. Cir. 1999). A breach of this duty constitutes inequitable conduct. *Molins*, 48 F.3d at 1178. If it is established that a patent applicant engaged in inequitable conduct, then the patent application is rendered unenforceable. *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 877 (Fed. Cir. 1988).

81. To establish unenforceability based on inequitable conduct, a defendant must establish, by clear and convincing evidence, that: (1) the omitted or false information was material to patentability of the invention; or (2) the applicant had knowledge of the existence and materiality of the information; and (3) the applicant intended to deceive the PTO. *Molins*, 48 F.3d at 1178. A determination of inequitable conduct, therefore, entails a two step analysis. First, the court must determine whether the withheld information meets a threshold level of materiality. A reference is considered material if there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. *Allied Colloids, Inc. v. American Cyanamid Co.*, 64 F.3d 1570, 1578 (Fed. Cir. 1995) (citations omitted). A reference, however, does not have to render the claimed invention unpatentable or invalid to be material. *See Merck & Co., Inc. v. Danbury Pharmacal*, 873 F.2d 1418, 1421 (Fed. Cir. 1989).

82. After determining that the applicant withheld material information, the court must then decide whether the applicant acted with the requisite level of intent to mislead the PTO. *See Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1327

(Fed. Cir. 2009); *Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1329 (Fed. Cir. 1998). "Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." *Herbert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). That is, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown*, 863 F.2d at 876. Evidence of specific intent must "be clear and convincing, and inferences drawn from lesser evidence cannot satisfy the deceptive intent requirement." *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008). A "smoking gun," however, is not required in order to establish an intent to deceive. *See Merck*, 873 F.2d at 1422.

83. Once materiality and intent to deceive have been demonstrated by clear and convincing evidence, the trial court must weigh them to determine whether the balance tips in favor of a conclusion of inequitable conduct. *N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1153 (Fed. Cir. 1987). The showing of intent can be proportionally less when balanced against high materiality. *Id.* In contrast, the showing of intent must be proportionally greater when balanced against low materiality. *Id.*

2. The '215 patent

a. The '215 patent's disclosure

84. The '215 patent discloses multiple examples of how to make an extended release version of methylphenidate. Of relevance to the suit at bar, the '215 patent discloses the following example that explains how to fabricate methylphendiate using a multi-layer extended release technology:

> Methylphenidate HCl (200 g) was slowly added to an aqueous solution (about 15% solids) of polyvinylpyrrolidone (10 g Povidone K-30) and mixed well. 25-30 mesh sugar spheres (770 g) were coated with the drug solution in a Versa Glatt fluid bed granulator. The drug containing pellets were dried, and a sealcoat of Opadry Clear (20 g) was first applied to produce IR Beads. ER Beads are produced by taking IR Beads and coating with the dissolution rate controlling polymer. A plasticized ethylcellulose coating was applied to the methylphenidate particles (893 g) by spraying Aquacoat® ECD-30 (233 g) and dibutyl sebacate (16.8 g). An outer seal coating formulation (20 g) of Opadry was sprayed onto the coated active particles. The coated particles were cured at 60° C for 12 hours so that polymer particles coalesce to form a smooth membrane on ER Beads.

('215 patent, col. 4:55-5:2)

b. The disclosure of the patents-in-suit

85. The patents-in-suit contain an example similar to the one found in the '215 patent, specifically:

> Cyclobenzaprine Hydrochloride (1,200 g) was slowly added to an aqueous solution of polyvinylpyrrolidone such as Povidone USP (K-29/32, 80 g) and mixed well. # 25-30 mesh sugar spheres (2,640 g) were coated with the drug solution in a Glatt fluid bed coater, equipped with a 9" bottom spray Wurster insert to provide IR beads with a coating weight of about 9%. The drug containing particles were dried, and a seal coat of OPADRY® Clear (2% w/w) was first applied and dried in the Glatt fluid bed unit as a precautionary measure to drive off excessive surface moisture. The composition and batch quantities of the IR Beads were given in 5 to 10 kg. Following the second coating process the IR Beads were passed through 14 and 25 mesh screens. Beads remaining on the 14-mesh screen were discarded as oversized beads and beads passing through the 25-mesh screen were discarded as undersized beads.
>
> The next step in the process was to apply an extended release polymer membrane by spraying AQUACOAT® ECD, an aqueous dispersion of ethylcellulose with dibutyl sebacate (76:24), onto the IR Beads for a weight gain of approximately 10%. The same fluid bed equipment was used to produce ER (extended release) Beads by further coating the AQUACOAT® coated beads with OPADRY® Clear for a weight gain of 2% w/w prior to curing at 60° C in a conventional oven for a period of 24 hours.

('793 patent, col. 8:22-47) This multilayered extended release formulation is then

claimed by the '793 patent. Specifically, claim 1 requires "an extended release coating comprising a water insoluble polymer membrane surrounding [an active ingredient core] (*Id.*, col. 10:30-31) "wherein said water insoluble polymer membrane comprises a water insoluble polymer selected from . . . ethylcellulose [and] . . . dibutyl sebacate." (*Id.* col. 10:48-59)

c. Materiality

86. Defendants contend that the '215 patent was material to the prosecution of the '793 patent because the '215 patent is directed to the same three-layer extended release technology claimed in the '793 patent, yet it was never submitted to the PTO during the prosecution of the '793 patent. (D.I. 233 at 52) The two patents describe the same extended release formulation for use with different (but structurally similar) active ingredients, and contain virtually identical examples. (D.I. 222 at 785:23-787:14) Defendants' expert, Dr. Gordon Amidon ("Amidon"), explained that a person of ordinary skill in the art would expect the cyclobenzaprine product to work in the '215 formulation based on methylphenidate working. (*Id.* at 787:5-14) Venkatesh's first few experiments confirmed this was the case. (D.I. 250:5-253:14)

87. Further evidencing that the '215 patent was relevant to the prosecution of the '793 patent was the fact that the same examiner who examined the '793 patent rejected claims in a child of the '793 patent as being obvious in light of the '215 patent. (D.I. 222 at 792:18-793:4; JTX5A at 4)

88. Plaintiffs respond that the '215 patent was not material because it is cumulative in light of International Patent Publication No. WO 99/12524 ("the '524 reference"). (D.I. 238 at 55) Plaintiffs' expert, Dr. Stanley Davis ("Davis"), explained

that the '524 reference is more material to the '793 reference because it discloses cyclobenzaprine, whereas the '215 patent does not and the '793 patent was rejected as being anticipated by the '524 reference. (D.I. 224 at 1391:22-1395:25)

89. Plaintiffs arguments are unpersuasive. As Amidon explained, the examples and formulations of the '215 patent and '793 patent were almost exactly the same.

> [You have] the same coating, same plasticizer. You also have the same clear coat. That's not so important. The same binder, polyvinyl pyrrolidone. Same mesh size for the starting sugar spheres. So these two examples are the same. The '215 patent is the same as the example in the '793 patent.
>
> . . .
>
> [As for the differences in the active ingredient and its effect on materiality,] these are both hydrochloride salts, both low dose. I mean, these are examples at different scales, but they're both soluble drugs. No. So the answer is no, it makes no difference to a formulation scientist[.] . . . [A] formulation scientist would expect the cyclobenzaprine product in this formulation to work based on methylphenidate working in this formulation.

(D.I. 222 at 786:20-787:14)

90. In contrast, Davis did not say that the '215 patent was cumulative to the '524 reference. Instead, he merely opined that the '215 patent was not relevant. (D.I. 224 at 1395:19-25) Given the substantial similarities between the '793 patent and the '215 patent, the court finds that an examiner would have found the '215 patent material to the prosecution of the '793 patent.

d. Intent

91. As with many cases of inequitable conduct, defendants do not have a smoking gun to prove intent. Instead, they rely on circumstantial evidence to support their claim. Defendants allege that Venkatesh knew of the '215 patent at the time of the '793 patent's prosecution because he a named inventor of the '215 patent and was also

touting the patent to potential Eurand customers during the same time frame. (D.I. 233 at 53; D.I. 220 at 314:7-14, 316:7-12) Defendants' only evidence of intent to deceive is that Venkatesh's other, less relevant, Eurand patents were submitted during prosecution of the '793 patent, while the '215 patent was the only one that was not.[16] (*Id.* at 54; D.I. 220 at 311:15-22)

92. Plaintiffs argue that an inference of deceptive intent "must not only be based on sufficient evidence and be reasonable in light of that evidence, but it also must be the single most reasonable inference able to be drawn from the evidence." (D.I. 238 at 57 *citing Cancer Research Tech. Ltd. v. Barr Labs., Inc.*, - F.3d -, 2010 WL 4455839, at *7 (Fed. Cir. Nov. 9 2010)) Here, plaintiffs contend that it is more reasonable to infer that the '215 patent was "off Eurand's radar" because it had been licensed to another company before the application that led to the '793 patent was filed. (D.I. 238 at 57)

93. Given the Federal Circuit's recent decision in *Cancer Research Technology Ltd. v. Barr Laboratories, Inc.*, 625 F.3d 724, 733 (Fed. Cir. 2010), the court cannot find intent to deceive when defendants' only evidence of intent is the fact that the '215 patent was not disclosed.

3. Prosecution counsel's misrepresentations to the PTO

94. In connection with compiling the information disclosure statement ("IDS") during prosecution of the '372 patent, counsel certified that, "after making reasonable inquiry," no item of information contained in the IDS was known to any individual for

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[16] Unlike the '215 patent, Venkatesh's other Eurand patents do not disclose the same thee-layer ER formulation as the '793 patent. (D.I. 222 at 785:23-787:117; D.I. 220 318:10-326:1)

more than three months before the IDS was filed. The IDS listed the '215 patent. Venkatesh was a named inventor on both the '215 and the '372 patents.

95. Although it is apparent that Venkatesh knew about the '215 patent more than three months before the IDS was filed, the court declines to hold the '372 patent unenforceable based on the disclosure of material prior art to the PTO.

III. CONCLUSION

For the reasons discussed above, the court concludes that both Barr and Mylan infringe each of the asserted claims of the patents-in-suit, and that they are not invalid for failure to disclose their best mode. Finally, the court finds that the patents-in-suit are invalid for being obvious.[17]

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[17] And, thus, are enabled, satisfy the written description requirement, and are not indefinitie.